Guidance for Industry and FDA Staff

Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

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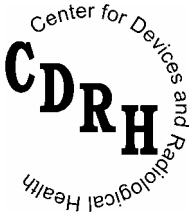

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Interventional Cardiology Devices Branch
Peripheral Vascular Devices Branch
Division of Cardiovascular Devices
Office of Device Evaluation

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at http://www.fda.gov/cdrh/ode/guidance/1545.pdf or you may either send a fax request to (301) 443-8818 to receive a hard copy of the document, or send an e-mail request to GWA@CDRH.FDA.GOV to request hard or electronic copy. Please use the document number (**1545**) to identify the guidance you are requesting.

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

Who should use this guidance?

All members of industry and FDA staff who perform or review non-clinical tests and prepare labeling of intravascular stents and their associated delivery systems should use this guidance. The terms "you" and "your" in this document refer to members of industry, also known as sponsors or applicants. The terms "we," "us," and "our" refer to FDA.

How should members of industry and FDA staff use this guidance?

Members of Industry

You should use this guidance to develop and apply non-clinical test protocols, test methods, and test reports that support the safety and effectiveness of intravascular stents and their associated delivery systems. You should also use this guidance to develop labeling for these devices.

FDA Staff

We should use this guidance to review non-clinical test protocols, test methods, data, and reports presented by sponsors in support of the safety and effectiveness of intravascular stents and their associated delivery systems. We should also refer to this guidance when we review the labeling for these devices.

What do the recommendations in this guidance mean?

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Does this guidance address the least burdensome approach to device applications?

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

Does this document supersede any other documents?

This document supersedes the information on stent and delivery system testing in the draft document "Carotid Stent - Suggestions for Content of Submissions to the Food and Drug Administration in Support of Investigational Devices Exemption (IDE) Applications," issued October 1996.[1]

Definition of Terms Used in this Guidance

Intravascular Stent

Intravascular stents are also known as endovascular stents or vascular stents. This document uses the term "intravascular stent" to refer to intravascular, endovascular, and vascular stents.

An intravascular stent is a synthetic tubular structure intended for permanent implant in native or graft vasculature. The stent is designed to provide mechanical radial support after deployment; this support is meant to enhance vessel patency over the life of the device. Once the stent reaches the intended location, it is expanded by a ballon or self-expanding mechanisms defined below.

Balloon Expandable Stent

A balloon expandable stent is expanded by a balloon catheter. The diameter of the stent increases as the balloon diameter increases. The stent remains expanded after deflation of the balloon.

[1] You may access this draft document at http://www.fda.gov/cdrh/ode/974.pdf. The recommendations in the draft document are not in effect.

Self-expanding Stent

A self-expanding stent's diameter increases from its pre-deployed size to its post-deployed size in the absence of balloon inflation or other mechanical assistance. The self-expanding quality can result from material properties or geometry or both.

Stent Delivery System

A stent delivery system delivers a stent to a target site and then deploys the stent. A stent delivery system for a balloon expandable stent consists of a balloon catheter. Self-expanding stent delivery systems may or may not include a balloon.

II. Background

Intravascular stents, including balloon expandable and self-expanding stents, are class III devices whose product codes are given in the table below.

Table 1: Product Codes for Stents Addressed in this Guidance

Product Code	Device
MAF	Stent, Coronary
NIM	Stent, Carotid
NIN	Stent, Renal
NIO	Stent, Iliac
NIP	Stent, Superficial Femoral Artery

These devices require a premarket approval (PMA) application before marketing. See sections 513(a) and 515 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR Part 814.

Clinical studies conducted in the United States in support of a PMA approval must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes that the intravascular stents addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m).[2] Such studies require an FDA-approved IDE and sponsors must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

After FDA has approved a device, clinical studies conducted in accordance with the indications in the approved PMA, including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the investigational device exemptions (IDE) requirements. However, such studies must be performed in conformance with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

[2] Refer to http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.

This guidance document supplements other FDA publications on PMA, PDP, and IDE applications and should not be construed as a replacement for those documents. For general information about these applications, see the CDRH Device Advice web site given below:

- PMAs (21 CFR Part 814): http://www.fda.gov/cdrh/devadvice/pma/
- PDPs (21 CFR § 814.19): http://www.fda.gov/cdrh/devadvice/pma/app_methods.html
- IDEs (21 CFR Part 812): http://www.fda.gov/cdrh/devadvice/ide/index.shtml.

This guidance also cites a number of voluntary standards, many of which are recognized by FDA. You may access a list of the FDA-recognized standards from the CDRH web site, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. See also the guidance, **Recognition and Use of Consensus Standards**, http://www.fda.gov/cdrh/ost/guidance/321.html.

III. Scope

What devices does this document address?

This guidance document addresses self-expanding and balloon expandable extracranial intravascular stents and their associated delivery systems. The scope includes extracranial intravascular stents placed in coronary, central, or peripheral arteries and saphenous vein grafts but is not limited to stents used in these locations; other vascular indications outside of the intracranial vasculature are also included.

What devices does this document NOT address?

Non-vascular stents meant for use outside the vasculature are not included in the scope of this document. This document also does not include stents used in the intracranial vasculature. You should contact the Division of Reproductive, Abdominal, and Radiological Devices for information about biliary stents or the Division of General, Restorative, and Neurological Devices for information about non-vascular stents and stents used in the intracranial vasculature.

Some of the tests (and labeling recommendations) in this guidance are relevant to covered, drug-eluting, and biodegradable stents, and stents used to treat aneurysms or dissections. However, FDA recommends additional testing to fully characterize these devices. The Interventional Cardiology Devices Branch and the Peripheral Vascular Devices Branch are available to discuss testing for these stents and indications.

IV. Purpose

This document provides guidance on the preparation and review of non-clinical test protocols, methods, data, reports, and labeling for intravascular stents and their associated delivery systems.

V. Content and Format of Test Data

What format should sponsors use to present test data?

We recommend that you present test data in a summary that includes the elements described below.

Table of Contents

You should place a table of contents at the front of the document. Each line listing in the table of contents should refer to major section titles and the page numbers where each section can be found.

Test Summaries

You should briefly describe all tests performed.

Test Data Summaries

You should include test data summaries for all tests. The summaries should contain:

- minimum measured value (min)
- maximum measured value (max)
- mean
- standard deviation of the test data (std. dev.).

Summary of Conclusions

You should summarize your conclusions as to whether the results support the safety and effectiveness of your device for each test.

You should include full test reports for all tests performed, as described below.

What information should sponsors include in test reports?

Your test reports should include the sections described below.

Test Specimen Information

Your test specimen description should include:

- number of test specimens
- size (diameter, length, or other relevant dimensions) of all test specimens
- rationale for the number of test specimens and sizes tested
- whether the specimens are representative of the finished product
- sterilization parameters and number of sterilization cycles applied to the test specimens.

Test Protocol

You should submit your test method or protocol. It should contain enough detail that an individual familiar with intravascular stent testing will be able to interpret the test results.

Protocol Deviations

You should describe any protocol deviations and their effect on the ability of the test data to support the safety and effectiveness of the device.

Test Parameters and Acceptance Criteria

You should report the test parameters and acceptance criteria that you use, including:

- an explanation of and rationale for critical test parameters
- specifications or acceptance and rejection criteria
- a rationale for the specification or acceptance and rejection criteria based on the clinical requirements of the device.

Raw Data

We recommend that you include all raw data in appendices or on a CD-ROM, or make the raw data available for our review upon request.

Test Results

You should summarize your test results and include statistical analysis when it is appropriate.

Data Analysis

You should analyze the data, including any outlying points and anomalous results, and explain whether the data meet the given acceptance criteria.

Conclusions

We recommend that you describe the conclusions drawn from the test results, and the clinical significance of the conclusions.

Should your tests have a test protocol?

Yes, you should establish protocols for all experiments or computational analyses, including acceptance criteria when applicable, before you perform the tests. Established test protocols help to ensure consistent repetition of tests and allow comparison of data between test runs.

We recommend that you present test protocols to us before conducting tests. We will review your protocol and provide comments. Our input before testing may improve your ability to demonstrate the performance characteristics of your device.

What information should test protocols contain?

Your test protocols should assess the most extreme clinical conditions that your device is likely to experience. Both device configuration and physiologic conditions affect the performance of devices in the human body. We recommend that you evaluate extreme device dimensions, tolerances, sizes, and any other important device parameters in your testing program. We also recommend that you examine the outer limits of physiologic variables such as blood pressure, vascular compliance, and anatomic types. You should clearly state all test conditions in the test protocol and support them with references to applicable literature, standards, or both.

Occasionally, the worst performing combination of device configuration and physiologic conditions occurs in the mid-range of the relevant variables. You should check for this situation when developing your protocols to ensure that you test the worst performing combination.

What if you believe a test is not applicable to your device?

The tests we are describing in this guidance are those we generally have reviewed in intravascular stent submissions and that we have considered necessary in the past to support the safety and effectiveness of these devices. However, some of the tests listed in this guidance do not apply to all intravascular stents and delivery systems. The designs or clinical indications to which these tests do apply are noted in their descriptions. We believe that each test helps to support the safety and effectiveness of intravascular stents. Each test's clinical or engineering significance is described in **Section VII**.

If you believe a test recommended in this guidance does not apply to your device, you should include a heading for the test in your test summary, followed by an explanation of why the test is not applicable. We will then be aware that you did not inadvertently omit it from your application.

Your explanation should include a rationale for why you do not think the test should be performed in order to support the safety and effectiveness of your device. Your rationale should clearly demonstrate, by reference to a Failure Modes and Effects Analysis (FMEA) or other risk analysis method, that the particular test or data set is not necessary or appropriate to support the safety and effectiveness of your device. Alternatively, you may identify measures you have taken to mitigate the risks associated with the device in the failure mode that would usually be tested using the test that you have not performed.

Intravascular stents have been in clinical use for over a decade and some designs are in their fourth or fifth generation. Some attributes may not depend on the changes made to a next-generation device. For a particular attribute, rather than providing original data for a next-generation design, it may be appropriate to reference previously tested stents in the same device family. We believe, however, that a reference to previous generic device experience, for example, "alloy X has been used in stents," generally is not adequate. If you choose to reference previously tested stents, you should explain why the previous testing is relevant.

What sample size should sponsors use for tests?

You should use a statistically significant sample size whenever possible. When using a statistically significant number of samples is not possible, you should provide a scientific rationale to support the number of samples tested in your test summary and test protocols, and provide reasonable assurance that the test results support the safety and effectiveness of the device.

Should sponsors test finished product?

All test samples should represent the finished product. Your devices should be sterilized by the final production process, including repeat sterilization cycles. You should note any tests that use samples that are not finished, sterilized product in the test summary and test protocols, and explain why doing so does not affect the ability of the test results to support the safety and effectiveness of the device.

What size devices should sponsors test?

You should test the full range of sizes that you intend to commercially distribute. The recommended default paradigm is a 2 x 2 factorial of the largest and smallest diameters and lengths, also known as the "four corners" paradigm for each different stent design. We recommend a different set of sizes for some of the tests in **Section VII. Table 2** illustrates the four corners concept for a typical coronary stent. If you do not test a device using the four corners paradigm or the recommended sizes for a particular test, you should provide a scientific rationale to support the sizes that you do test in the test summary and test protocols. For some tests, we may recommend that you perform an analysis to identify the size or sizes that represent the worst case.

Table 2: Four Corners Test Paradigm Example

Stent Diameter (mm)	**Stent Length (mm)**			
	8	12	18	24
2.5	X			X
3.0				
3.5				
4.0	X			X

VI. Risks to Health

FDA has identified some of the risks generally associated with the use of the intravascular stents addressed in this document. The preclinical and labeling measures recommended to address these risks are given in this guidance document. You should conduct a risk analysis to identify other risks specific to your device, and include the risk analysis in your application. The application should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or you have identified risks in addition to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

VII. Non-Clinical Tests

A. Material Characterization

1. Material Composition

Significance

Material composition testing documents a baseline for evaluation of the effects of future changes in materials.

Recommendation

We recommend that you specify the device characteristics described below. If your stent material is identical to your previously marketed stents, we recommend that you identify the stent(s) and material(s) to which it is identical.

Stent and Delivery System Materials

We recommend that you list materials by trade or common name, for example, 316L stainless steel.

Generic Chemical Formulation

We recommend that you list formulations of all materials by generic name, for example, 18 Cr-14 Ni-2.5 Mo stainless steel. We recommend that you reference any applicable standard designations such as ASTM F138.

Chemical Composition and Formulation

We recommend that you provide detailed specifications for the chemical composition or formulation of materials (or both) for any new materials, alloys, or formulations with no history of use in intravascular stents or PTCA catheters.

Material Certification

We recommend that you provide documentation to certify that incoming raw material conforms to specifications. We recommend that you submit supplier certification, incoming quality control test results, or equivalent documentation.

2. Shape Memory and Superelasticity of Intravascular Stents

Significance

The transition temperature of nitinol or other shape memory and superelastic materials determines specific shape memory and superelastic properties.

Recommendation

We recommend that you document the following properties for any shape memory or superelastic materials present in your stent.

Austenite Finish Transition Temperature (Af)

We recommend using the methods described in ASTM F2004, ASTM F2082, or equivalent methods.

Mode of Action

We recommend that you describe the mode of action, for example, thermal shape memory or superelasticity, that the stent undergoes to achieve the specified size and shape.

3. Stent Corrosion Resistance

Significance

Stent corrosion can cause or contribute to premature stent failure. In addition, corrosion byproducts may be toxic or cause other adverse biological and tissue responses.

Recommendation

We recommend that you address the corrosion properties of your device described below. If some of these characteristics do not apply to your device, we recommend that you explain this in your application.

Pitting and Crevice Corrosion Potential

We recommend that you characterize the corrosion potential of your finished stent using a method such as ASTM F2129.

You may use literature citations or previous experience with stents; however, the materials, design, and fabrication processes specific to your stent may reduce or eliminate the applicability of generic literature. For example, the pitting corrosion resistance of nitinol is sensitive to processing variables such as heat treatment and

electropolishing; therefore, for a nitinol stent, you should characterize the corrosion potential of the finished stent.

Fretting Corrosion

We recommend that you address the potential for fretting corrosion in designs that allow micromotion between components, such as woven wires, that may disrupt an associated coating or passive film. If you expect that your stents will be overlapped during clinical procedures, then we recommend that you address the possibility of the additional risk of stent failure caused by fretting corrosion. If you believe that overlapping your stents does create an additional risk, then we recommend that you test overlapping stents as part of the corrosion experiment.

Galvanic Corrosion

If your stent contains more than one type of metal, such as a base stent material with added marker bands, we recommend that you demonstrate the design's resistance to galvanic corrosion. If you expect that your stents will be overlapped during clinical procedures, and the contacting or overlapping stents may be made of different materials, we recommend that you address the potential for galvanic corrosion between stents. We recommend the methods described in ASTM G71 or their equivalents. These methods may be modified to provide for testing of finished stents, for example, by incorporating the experimental setup described in ASTM F2129.

B. Stent Dimensional and Functional Attributes

1. Dimensional Verification

Significance

Accurate stent dimensions help the physician to achieve proper stent sizing and accurate placement in the body. They also affect the functional behavior of the stent.

Recommendation

FDA recommends that you provide the information described below that applies to your stent. We recommend the methods used in ASTM F2081 or their equivalents.

Un-expanded Stents

We recommend that you provide dimensional specifications and tolerances for un-expanded stents. You do not need to submit actual test data. We recommend that you reference this information in any sections of the application that do not relate to preclinical testing, such as the manufacturing section or the device description.

Balloon Expandable Stents

We recommend that you measure and report the expanded diameter of balloon expandable stents. You may do this as part of the process of creating a

compliance chart. See section **C. Delivery System Dimensional and Functional Attributes, 4. Stent Diameter vs. Balloon Pressure**.

Self-Expanding Stents

We recommend that you verify the unconstrained expanded diameter of self-expanding stents with measurement data.

2. Percent Surface Area

Significance

The area over which a stent contacts a vessel may affect the biologic response of the vessel. The amount of open, non-contact area may influence tissue prolapse or ingrowth.

Recommendation

We recommend that you report the percent surface area of the stent for both the smallest and largest nominal expanded diameters for each stent design. We recommend that you evaluate different lengths only if you expect that the percent surface area varies significantly with stent length. We recommend that you measure or calculate the contact area of the stent structure, and express the final value as a percentage of the reference area. (The reference area is defined as the full cylindrical surface area at the expanded stent diameter.) We recommend that you apply the methods described in ASTM F2081 or their equivalents.

3. Foreshortening

Significance

Foreshortening, i.e., dimensional changes that may occur when deploying a stent, influences final stent length. Knowledge of the foreshortening characteristics aids in proper stent length selection and proper placement in the body.

Recommendation

FDA recommends that you report the decrease in length of the stent between the catheter-loaded condition and the deployed diameters up to the maximum labeled diameter.

We recommend that the reported value reflect the maximum nominal diameter. We recommend that you report the results in terms of a percentage of the loaded length as shown below:

$$\text{Percent Foreshortening} = 100 \times (\text{Change in Length} \div \text{Loaded Length}).$$

We recommend that you apply the methods described in ASTM F2081 or their equivalents.

See section **VIII. Labeling** for recommendations on data presentation of the percent foreshortening of self-expanding stents.

4. Recoil for Balloon Expandable Stents

Significance

The recoil behavior of balloon expandable stents influences proper device selection, sizing, acute post-implant results, and long-term clinical outcomes. Recoil is a function of stent design and material selection; therefore, knowledge of stent recoil helps to characterize the behavior of a particular stent design.

Recommendation

We recommend that you report the measured change in diameter of your stent between post-balloon expansion and after balloon deflation.

We recommend that you measure and report values for each labeled stent diameter. If you expect that the percent recoil varies significantly with length, we recommend that you evaluate different stent lengths.

We recommend that you present the results as a percentage of the expanded diameter.

We recommend the methods described in ASTM F2079 or their equivalents.

5. Stent Integrity

Significance

Stent defects, whether a result of manufacturing flaws or subsequent damage, can contribute to clinical complications. Laser cutting or other manufacturing processes may induce flaws that are not completely removed by polishing. Plastic deformation during loading or balloon expansion may cause cracks or other damage. Self-expanding stents that are stored loaded in a delivery system may exhibit permanent set or changes in expansion characteristics as a result of time or sterilization or both.

Recommendation

We recommend that you examine your deployed stent and report any evidence of stent defects such as, but not limited to:

- cracks
- scratches
- permanent set
- coating delamination.

We recommend that you use optical or electron microscopy, or both to look for defects. We recommend that you support the level of magnification that you use on the basis of the size of the defect that your inspection attempts to detect.

When you are looking for post-deployment damage, we recommend that you examine or inspect:

- balloon expandable stents, after expansion to the largest diameter listed in your labeling
- self-expanding stents, after expansion to the unconstrained diameter.

6. Radial Stiffness and Radial Strength

Significance

Radial stiffness and stent recoil determine the diameter of balloon expandable stents deployed in compliant vessels. Radial stiffness and radial strength characterize the ability of the stent to resist collapse under short-term or long-term external loads.

Recommendation

We recommend that you report a value for your stent's radial stiffness, i.e., the change in stent diameter as a function of uniformly applied external radial pressure. We recommend that you also report a value for radial strength, i.e., the pressure at which your stent experiences irrecoverable deformation.

FDA recommends that you measure and report values for each labeled stent diameter. If you expect that the radial stiffness varies significantly with length, we recommend that you evaluate different stent lengths.

We recommend that you support the diameter or pressure range used in your tests for radial stiffness. The diameter and pressure range will probably vary depending on your stent's intended target site.

7. Mechanical Properties

Significance

Raw material properties determine incoming material quality and uniformity, and predict subsequent thermomechanical effects. Thermomechanical properties of the implanted stent affect clinical performance, as well as stress and fatigue behavior.

Recommendation

We recommend that you specify the mechanical properties listed below for the stent raw material(s).

Mechanical Properties of the Raw Material(s)

- ultimate tensile strength (UTS)
- yield strength (YS)

- elongation
- plateau stresses, for nitinol
- elastic strain limits, for nitinol.

Post-Processing Mechanical Properties

FDA also recommends that you report the stress-strain response of the stent after deployment. We recommend that you present the stress-strain behavior in a plot or graph that shows both loading and unloading. We recommend that you report the following post-processing mechanical properties of your stent:

- UTS
- YS
- elongation
- elastic modulus
- Poisson ratio
- endurance limit
- plateau stresses, for nitinol
- elastic strain limits, for nitinol.

In addition, reporting other mechanical properties at previous stages of manufacture, may allow characterization of your material for use in your stress analysis. See section **8. Stress Analysis**. We recommend that you determine the stress-strain response, endurance limit, and post-processing mechanical properties through physical experiments or computational models that simulate stent material properties, manufacturing, and deployment processes. If you cite any quoted literature or handbook values, we recommend that you explain how they are relevant to your device. We also recommend that you use and reference standard test methods whenever possible, and describe any nonstandard test methods in detail.

8. Stress Analysis

Significance

Failure of a loaded stent may result in loss of radial support of the stented vessel or in perforation of the vessel by the stent struts. Stress analysis, combined with fatigue analysis and accelerated durability testing, provides an indication of device durability.

Recommendation

FDA recommends that you include the following elements in your stress analysis and test report for each stent design.

Modeled Stent Sizes

If you do not model all of your stent sizes, explain why the modeled stent size is the worst case with respect to critical stresses.

Analytical Model and Inputs

We recommend that you clearly identify and explain the sources and values of all inputs and assumptions used to create the analytical model. Identify any software used for analysis. We recommend that finite element analysis reports include the element types used to model the stent, loading surfaces, and boundary conditions.

Physiologic Loading Conditions

We believe that most coronary stents can be modeled using radial dilation as the only loading condition.

For non-coronary stents, long stents, and coronary stents used for new indications or locations in the body, we recommend that you determine the loading conditions.

Physiologic loading will depend on the implantation site and may include, but is not limited to:

- radial dilation
- torsion
- bending
- axial tension
- axial compression
- crushing, including focal, non-focal, or uniform radial compression.

We recommend that you address the list above as well as any other relevant loading conditions when you develop the model for your stent.

Stress History

FDA recommends that you include the entire stress history of the device in each loading step. The entire stress history may include, but is not limited to:

- initial fabrication
- expansion
- loading onto the delivery system
- deployment
- physiologic loading conditions.

If you believe that you do not need to model the entire stress history, we recommend that you use material properties that are consistent with the starting point of your analysis. We recommend that the material properties accurately reflect the processing history of the stent as described in **7. Mechanical Properties**. We also recommend that you explain why the omitted loading steps either do not affect the stent fatigue life or are accounted for in your model.

Temperature Dependent Behavior

We recommend that you model any temperature dependent behavior of the stent.

Stress Critical Locations and Magnitude

We recommend that you identify the critical locations of stress on the stent using finite element analysis or another stress analysis method and address the effect of dimensional variation within allowable tolerances on the maximum critical stress that the stent will experience. We recommend that you report the location and magnitude of all maximum tensile and compressive stresses and strains using graphics.

If you choose to perform a strain based analysis instead of a stress based analysis, we recommend that you explain why the strain based analysis is more appropriate for your device.

9. Fatigue Analysis

Significance

Failure of a stent due to fatigue may result in loss of radial support of the stented vessel or in perforation of the vessel by the stent struts. Fatigue analysis, combined with stress analysis and accelerated durability testing, provides an indication of device durability.

Recommendation

FDA recommends that you determine the fatigue resistance of the stent to physiologic loading using a Goodman analysis or another fatigue life analysis method. We recommend that your test report include the following elements.

Modeled Stent Sizes

If you do not analyze all stent sizes, we recommend that you explain why the modeled stent size is the worst case for fatigue life.

Inputs and Assumptions

FDA recommends that you use the mean and alternating stresses obtained from the stress analysis as input for the fatigue life determination. We recommend that you clearly identify and support all inputs and assumptions used in your analysis. If you use literature values for any material properties, we recommend that you identify the source of the data and support that your values correspond to the as-implanted condition of the material.

Results

We recommend that you provide a Goodman diagram or other graphic that compares the stresses at critical locations in the stent to the mechanical properties of the stent material. We recommend that you report fatigue safety factors in a table and explain how the safety factors were calculated.

If you choose to perform a strain based analysis instead of a stress based analysis, we recommend that you explain why the strain based analysis is more appropriate for your device.

10. Accelerated Durability Testing

Significance

Accelerated durability testing validates fatigue analysis. It evaluates failure modes such as fretting, abrasion, and wear. Durability testing can help in the identification of device conditions, such as manufacturing anomalies, that were not modeled using analytical or computational methods.

Recommendation

FDA recommends that accelerated durability testing of your stent address the following issues.

Sample Size

We recommend that you determine sample size based on your fatigue analysis, including boundary conditions, loading conditions, safety factors, and any other relevant factors.

We recommend that you consider a stent as one test specimen when you report reliability calculations and results. We recommend that you consider the stent as one test specimen regardless of the symmetries present in apices, repeat units, or struts of the stent.

Sizes Tested

We recommend that you select and support the stent size or sizes tested based on the stress and fatigue analyses or other factors. We recommend that the sizes tested represent the worst case fatigue life of your device.

Test Duration

We recommend that you test the durability of your stent to the equivalent of ten years of real-time use under pulsatile flow and physiologic loading that simulates blood pressure conditions in the human body. We believe that ten years of durability data provides sufficient proof of safety of the device for most patients. If you perform a rigorous and conservative fatigue analysis that indicates an acceptable analytical safety factor, you may propose to complete long-term durability testing concurrent with clinical trials and to submit the final results in your PMA.

Loading and Boundary Conditions

FDA recommends that you perform long-term durability testing that models the physiological loads and boundary conditions that your stent is likely to experience under its intended use.

We recommend that you address any other types of cyclic loading, such as flexure, that you anticipate your stent will experience when used as intended, and incorporate these types of loading into your testing where possible. We recommend that you explain the clinical relevance of the loading conditions used for the accelerated durability testing. If the conditions you choose differ from the loading conditions that you modeled in the stress and fatigue analyses, we recommend that you report and explain the differences.

Overlapping Stents

If you expect that your stents will be overlapped during clinical procedures, we recommend that you address the possibility of the additional risk of stent failure caused by wear or other factors. If you believe that overlapping your stents does create an additional risk, then we recommend that you test overlapping stents as part of the durability experiment.

Results

We recommend that you relate the outcome of your test to the stress and fatigue analysis results.

11. Magnetic Resonance Imaging (MRI) Safety and Compatibility

Significance

MRI of patients with stents poses the following potential hazards:

- heating of the implant and subsequent tissue damage
- movement of the implant, resulting in tissue damage or misplacement
- imaging difficulties resulting in inappropriate medical treatment.

In addition, we are concerned that a large population of patients may receive inadequate treatment if radiologists choose not to perform MRI on a patient because of their uncertainty about the possibility of migration in a stent with characteristics that may affect time to endothelialization.

Recommendation

FDA recommends that you address the issues affecting safety and compatibility of your stent in the MRI environment as described below.

Magnetically Induced Force and Torque

We recommend the methods described in ASTM F2052 and ASTM F2213 or their equivalents.

Image Artifacts

We recommend the methods described in ASTM F2119 or equivalent.

Radiofrequency (RF) Heating

We recommend the methods described in ASTM F2182 or equivalent.

Test Environment

We recommend that you report details of the test environment, such as, but not limited to:

- magnetic field strength in Tesla (T)
- spatial gradient
- time rate of change of magnetic field (dB/dt)
- specific absorption rate (SAR).

We recommend that you use the highest widely available field strength (currently 3T) and worst case conditions for your testing. As systems with higher field strengths become available, we recommend they be used as the most current worst case.

Bare Metal Stents

If you demonstrate that your bare metal stent is identical in materials and similar in design to previously marketed stents with a history of successful use that have demonstrated MRI safety at commonly used field strengths you may reference literature or previous clinical or non-clinical experience in place of performing further tests. When you use literature references instead of actual test data, we recommend that you describe any differences between your stent and the referenced stent such as mass, geometry, or manufacturing methods (for example, a change to the amount of cold work).

If these differences could affect the MRI compatibility, we recommend that you test your stent. For example, if the amount of cold work has significantly increased, we recommend that you perform a deflection force test.

If information to evaluate differences between your stent and the referenced stent is not available, we recommend that you test your stent. We also recommend that you test your stent if it is made of a novel material or if it is a design without a history of successful prior use. We recommend the procedures described in ASTM Methods F2052, F2213, F2119, and or F2182, or their equivalents.

Stents with Characteristics that Affect Time to Endothelialization

We recommend that you perform MRI migration testing for force and torque on stents with coatings or other attributes that may increase endothelialization time, such as drug-eluting stents. If your stent meets the acceptance criteria in ASTM 2052 and ASTM 2213 or an equivalent set of test methods, you may report your results without further testing. If your stent does not meet the recommended acceptance criteria in these or equivalent methods, we recommend that you determine the time to full endothelialization for your stent and determine whether the stent meets the criteria in ASTM 2052 and ASTM 2213 or their equivalents after endothelialization.

Stents with Certain Indications

For stents with indications where MRI is used to rule out common adverse events (for example, carotid stenting where MRI is used to look for strokes), we recommend that you perform MRI migration testing for force and torque. We recommend that you perform this testing at commonly used field strengths. If your stent meets the acceptance criteria in ASTM 2052 and ASTM 2213 or an equivalent set of test methods, then you may report your results and we do not recommend any further testing. If your stent does not meet the recommended acceptance criteria in these or equivalent methods, we recommend that you provide information from clinical or animal testing to determine whether MRI post-implantation results in any associated clinical sequelae.

We recommend that your labeling contain information for the patient and medical personnel about any potential hazards that MRI may have as a result of the implant. See section **VIII. Labeling**, for examples of language describing the MRI compatibility of stents in labeling.

12. Radiopacity

Significance

Stent visibility using angiographic or radiographic imaging or both generally assures proper stent placement and allows follow-up and secondary treatment.

Recommendation

FDA recommends that you evaluate the radiopacity of your stent at the smallest diameter and the shortest length during the following stages in the life of the stent:

- delivery
- deployment, if separate from delivery
- after implantation.

We recommend that you provide a qualitative or quantitative indication of the visibility of the stent on real-time and plane film x-ray. It is acceptable to compare device or calibration artifact data from images of animal implants, *in vitro* phantoms, or equivalent models.

13. Coating Durability (Coated Stents Only)

Significance

Premature delamination or degradation of a coating may lessen its benefit. Embolized particulate may present clinical complications. Flaws in a coating may increase susceptibility to corrosion.

Recommendation

FDA recommends that you report on the aspects described below of any coatings applied to the surfaces of your stent.

Physical Structure and Chemical Properties

We recommend that you describe the aspects of the coating's physical structure, such as coating thickness, as well as chemical characterization.

Intended Function

We recommend that you describe the purpose and intended function of the coating. Examples of intended functions include, but need not be limited to:

- enhanced radiopacity
- enhanced thrombogenicity
- matrix for drug elution.

We recommend that you also explain the clinical benefit of the coating.

Loading History

We recommend that you evaluate the stent for coating durability at the following time points for each coating durability test:

- before expansion
- after expansion to the largest labeled diameter
- after accelerated durability testing
- after simulated use.

We recommend that you state the intended lifetime of the coating and evaluate the ability of the coating to remain integral with the stent over time.

Coating Stress Analysis

We recommend that you perform a finite element or other stress analysis of the coating and identify the location of critical areas where the stent experiences maximum stress.

Particle Count or Analysis Methods

If you evaluate coating durability using particle count or analysis methods, or both, we recommend that you address the clinical significance of the number and size of observed particles.

Coating Adhesion and Cohesion

We recommend that you perform testing to measure the adhesion of the coating to the stent as well as cohesion between multiple coating layers. We recommend that you report the results of such testing for both single and multi-layer coatings, and coatings that involve the use of a primer to promote coating adhesion to the stent.

Corrosion Resistance

FDA recommends that you evaluate the effects of cracked or de-laminated coatings on corrosion resistance. We recommend that you perform corrosion testing after inducing a flaw in the coating, and that the flaw completely penetrate the coating down to the base material of the stent. We recommend testing according to the methods described in ASTM F746 or an equivalent method. You may modify the method to test the finished, flawed stent; for example, by incorporating the experimental setup described in ASTM F2129.

We recommend that you address the potential for fretting corrosion in designs that allow micromotion between components, such as woven wires, which may disrupt an associated coating or passive film. If you expect that your stents will be overlapped during clinical procedures, then we recommend that you address the possibility of the additional risk of stent failure caused by fretting corrosion. If you believe that overlapping your stents does create an additional risk, then we recommend that you test overlapping stents as part of the corrosion experiment.

Additional Testing

Although many tests in this guidance are relevant to covered, drug-eluting, and biodegradable stents, FDA recommends additional testing to fully characterize the integrity of drug-eluting and other biodegradable stent coatings. We recommend that you assess the need for additional testing to address coating integrity for drug-eluting stents or biodegradable coatings. The Interventional Cardiology Devices Branch and the Peripheral Vascular Devices Branch are available to discuss coating integrity testing for these stents.

14. Crush Resistance (Peripheral Indications Only)

Significance

Peripheral stents in some anatomic locations may experience external, non-cardiac, focal, or distributed loads. These loads could cause stent deformation and, possibly, adverse clinical consequences.

Recommendation

FDA recommends that you demonstrate the ability of your stent to recover its desired size and shape after application and removal of external loads, deformations, or both. We recommend that you support the nature, location, and extent of all external loads and deformations based on the intended implantation site, for example, the carotid or femoral arteries.

We recommend that you report the change in unloaded stent dimensions after the application and removal of all of the specified loads and displacements.

15. Kink Resistance (Peripheral Indications Only)

Significance

Peripheral stents used in some anatomic locations will bend during normal body motion, such as knee flexion. Such bends could cause stent deformation and possible adverse clinical consequences.

Recommendation

We recommend that you determine the smallest radius of curvature that your stent can withstand without kinking, and demonstrate that the stent recovers its original size and shape after testing. We recommend that you support the nature, location, and extent of all external loads and deformations based on the intended implantation site, for example, the carotid or femoral arteries.

C. Delivery System Dimensional and Functional Attributes

1. Delivery, Deployment, and Retraction

Significance

The delivery catheter should safely and reliably deliver the stent to the intended location according to the instructions for use, without damage to the stent.

Recommendation

FDA recommends that you test that the delivery catheter can safely and reliably deliver the stent to the intended location. We also recommend that you demonstrate that the stent is not adversely affected by the delivery catheter, both during deployment and withdrawal. We recommend that you also perform any tests that provide the performance characteristics described in your labeling and other instructions for use. Unless otherwise noted, we recommend that you conduct all testing on complete sterilized assemblies with mounted stents. We also recommend that you thermally equilibrate all test samples in a 37°C saline bath.

2. Balloon Rated Burst Pressure (Balloon Expandable Stents Only)

Significance

The rated burst pressure (RBP) is the pressure at which 99.9% of balloons can survive with 95% confidence. Failure of a balloon to survive at the RBP could result in an adverse clinical outcome.

Recommendation

We recommend that you test balloons with mounted stents that are not constrained by any test fixture, such as tubing. If the entire range of device sizes will have a single labeled RBP we recommend that you conduct testing on the longest length of every balloon diameter, plus the smallest diameter at the shortest length and the largest diameter at the shortest length. **Table 3** illustrates the recommended test matrix.

Table 3: Stent Delivery Sizes to Test for RBP

Stent Diameter (mm)	Stent Length (mm)			
	8	12	18	24
2.5	X			X
3.0				X
3.5				X
4.0	X			X

We recommend that you test according to the example in **Table 3** for each balloon size with a different labeled RBP. We recommend that you increase balloon pressure in uniform increments until failure.

We recommend that you record as test failures any loss of:

- integrity of the balloon, such as a rupture or leak
- pressure due to failure of the balloon, shaft, or seals.

We recommend that you record the pressure at which the device failed and the failure mode. We also recommend that you calculate RBP as the pressure at which 99.9% of the balloons will survive with 95% confidence based on statistical analysis of the test data.

3. Balloon Fatigue (Balloon Expandable Stents Only)

Significance

Balloons on stent delivery systems are often inflated multiple times during clinical use. Failure of the balloon to withstand multiple inflations could lead to adverse clinical consequences.

Recommendation

FDA recommends that you determine the repeatability, to 10 inflations, of successful balloon inflation to the RBP. We recommend that your sample dimensions follow the four corners paradigm:

- largest and smallest diameters
- largest and smallest lengths.

We recommend that you test balloons with mounted stents that are not constrained by any test fixture such as tubing and that you inflate the balloons in increments until they reach the RBP. For each sample we recommend that you hold the RBP for 30 seconds (or the time specified in the instructions for use), deflate the balloon, and inflate it again to the RBP, for a total of 10 cycles. We recommend that you report any loss of pressure, whether due to failure of the balloon, shaft, or proximal or distal seals, as a test failure. We recommend that you record all failure modes, and that your results demonstrate that 90% of the balloons will survive the test with 95% confidence.

4. Stent Diameter vs. Balloon Pressure (Compliance Chart) (Balloon Expandable Stents Only)

Significance

The diameter of a deployed balloon expandable stent varies with the applied balloon pressure. A compliance chart in the labeling that relates stent diameter to balloon pressure guides selection of stent size to fit the target lesion.

Recommendation

FDA recommends that you test all stent diameters at their longest lengths. We recommend that you clearly state and explain why you chose the test sample size. **Table 4** below illustrates the recommended test matrix.

Table 4: Recommended Test Matrix for Stent Diameter vs. Balloon Pressure.

Stent Diameter (mm)	**Stent Length (mm)**			
	8	12	18	24
2.5				X
3.0				X
3.5				X
4.0				X

We recommend that you submit a graphical or tabular presentation of inflation pressure vs. stent inner diameter (ID), i.e., a compliance chart, over the full range of recommended deployed stent diameters, and report the final results in the instructions for use, the outside package labeling, or both. We recommend that you identify the nominal inflation pressure and RBP. The compliance chart may include pressures up to 25% higher than the RBP, if you provide data and statistics demonstrating that

99% of the balloons will not fail at the listed pressure with 95% confidence. We recommend that you test multiple product lots. We also recommend that you clearly document any data rounding. **Table 5** below shows a sample compliance chart for a stent with 3.0 mm, 3.5 mm, and 4.0 mm diameters, with a RBP of 16 atmospheres (atm). The nominal diameter occurs at 9.0 atm.

Table 5: Sample Compliance Chart for a Balloon Expandable Stent

Pressure (atm)	Stent Nominal Diameter where x = stent inner diameter at the given pressure		
	3.0 mm Stent Inner Diameter (mm)	3.5 mm Stent Inner Diameter (mm)	4.00 mm Stent Inner Diameter (mm)
9.0	x	x	x
10.0	x	x	x
11.0	x	x	x
12.0	x	x	x
13.0	x	x	x
14.0	x	x	x
15.0	x	x	x
16.0*	x	x	x

*RBP

5. Catheter Bond Strength

Significance

Failure of bonds in the delivery catheter could lead to device failure and clinical complications.

Recommendation

We recommend that you test the bond strength at locations where adhesives, thermal fusion, or other joining methods are used for bonding components of the delivery system.

6. Crossing Profile

Significance

Stent delivery system crossing profile influences the device's ability to cross lesions.

Recommendation

FDA recommends that you measure and report the crossing profile of your delivery system, defined as the maximum diameter found between the proximal end of the mounted stent and the distal tip of the delivery system.

We recommend that you report the crossing profile in the instructions for use, the outside package labeling, or both. We recommend the methods described in ASTM F2081 or their equivalents.

7. Balloon Inflation and Deflation Time (Balloon Expandable Stents Only)

Significance

Balloons occlude the target vessel and obstruct blood flow while inflated. Inflation and deflation times affect occlusion time. Excessively slow deflation of a balloon could lead to adverse clinical consequences.

Recommendation

FDA recommends that you specify the balloon's inflation and deflation times and demonstrate, using non-clinical testing, that the balloon inflates and deflates within those times. We recommend that you observe and describe any interference with balloon deflation or delivery system extraction from the deployed stent.

8. Stent Securement for Unsheathed Stents

Significance

Dislodgment of the stent prior to deployment can result in stent embolization. Stents without sheaths may dislodge if they catch on tortuous anatomy, guide catheters, or other devices.

Recommendation

FDA recommends that you evaluate the force that will dislodge the stent from the delivery system under clinically relevant conditions. We recommend that the test simulate the intended use, including insertion through a tortuous path that simulates the vasculature proximal to the lesion site. We recommend that the tortuous path be sized appropriately for the stent size being tested. We recommend that you submit a photo, diagram, or description of the tortuous path, including dimensions. We recommend that the stent sizes tested represent the worst case stent securement for your design. We recommend that you explain why your results are applicable to all sizes of your stent, including those not tested for stent securement.

FDA recommends that you address the modes of dislodgement as described below:

Dislodgement by Forward Motion

Advancing a stent delivery system across a tight lesion could result in stent dislodgement. We recommend testing the stent by passing it through a simulated tight lesion in the tortuous path.

Dislodgement by Reverse Motion

Withdrawing a stent delivery system into a guiding catheter, arterial sheath, or hemostasis valve could result in stent dislodgement. We recommend testing the stent by attempting to withdraw the un-deployed stent into a guide catheter or other opening of the smallest size recommended in the instructions for use.

D. Biocompatibility

Significance

Stent and delivery systems contain patient-contacting materials, which when used for their intended purpose, i.e., contact type and duration, may induce a harmful biological response.

Recommendation

We recommend that you determine the biocompatibility of all patient-contacting materials present in your device. If your materials are identical in composition and processing methods to materials with a history of successful use in cardiovascular implant applications, you may reference the appropriate literature or previous clinical experience. We recommend that you test novel materials, i.e., those with no history of successful prior use according to the methods in the FDA-recognized version of ASTM F748 or the FDA-recognized sections of ISO 10993. We recommend that you follow the guidance **Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing**[3]

VIII. Labeling

General labeling requirements for medical devices are described in 21 CFR Part 801. Additional information may be obtained from Device Advice http://www.fda.gov/cdrh/devadvice/. You must submit all proposed labeling in your PMA. 21 CFR 814.20(b)(10).

FDA recommends that labeling for extracranial intravascular stents include the sections described below. These recommendations reflect the labeling that we have considered necessary in that past to support the safety and effectiveness of these devices and are consistent with labeling of currently marked intravascular stents. Some of these recommendations may also be relevant to covered, drug-eluting, and biodegradable stents; however, FDA recommends additional labeling, not described in this document, for those devices. The Interventional Cardiology Devices Branch and the Peripheral Vascular Devices Branch are available to discuss labeling for those stents and indications.

A. Device Description

We recommend that you describe the stent and delivery catheter, including the stent material, whether the stent is balloon expandable or self-expanding, etc. You should consider including a table with the following attributes, as appropriate:

- available stent diameters and lengths
- guiding catheter compatibility
- deployment and RBPs
- percent stent free area.

[3] http://www.fda.gov/cdrh/g951.html

We recommend that you describe any ancillary or accessory devices that are packaged with your stent system when no separate labeling is available. An example would be a description of an embolic protection system that is packaged with your stent delivery system. You may add additional information where appropriate.

B. Indications for Use

We recommend that proposed labeling reflect the precise indications for use statement that is the subject of the application. The general statement of the "Indications for Use" identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.

C. Contraindications

We recommend that you include contraindications to the use of the device. Contraindications describe situations in which the device should not be used because the risk of use clearly outweighs any possible benefit.

D. Warnings

We recommend that you include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.

We believe a warning is also appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition and use of the device is associated with a serious risk or hazard.

We also recommend that you include warnings to address the:

- need for appropriate anticoagulation or antiplatelet therapy or both
- recommendation that when multiple stents are used, they should be of similar composition
- fact that long-term outcomes following repeat dilatation of endothelialized stents are unknown.

E. Precautions

You should include as precautions information regarding any special care physicians or others should exercise for the safe and effective use of the device. Additionally, you should include any limitations on the use of a device for reasons including, but not limited to:

- lack of long-term safety and effectiveness data
- lack of safety and effectiveness data for special patient populations
- need for appropriate physician training

- anatomical or physiological limitations on the effectiveness of the device.

Stent handling, stent placement, stent system removal, and any post-implant precautions are appropriate for inclusion in this section. Additionally, you should address length of follow-up or use in special patient populations, for example:

> The safety and effectiveness of the ABC (coronary or peripheral) stent system has not been established in patients beyond x (months/years) of follow-up.
>
> or
>
> The safety and effectiveness of the XYZ coronary stent system has not been established in patients with recent acute myocardial infarction.

F. MRI Compatibility

We recommend that your labeling contain information for the patient and medical personnel about any potential hazards that MRI may present as a result of the implanted stent. We recommend that labeling describing the MRI compatibility of your stent be based on whether you have tested the effects of force, torque, and radiofrequency (RF) heating in the MRI environment. For the recommended testing, see section **VII. Non-Clinical Tests, B. Stent Dimensional and Functional Attributes, 11. Magnetic Resonance Imaging (MRI) Safety and Compatibility**.

Stents Tested for Force, Torque, and Heating

If you have tested for force, torque, and heating, successfully, we recommend that your labeling describe the testing and results, for example:

> Through non-clinical testing, the ABZ stent has been shown to be MRI safe at field strengths of x Tesla or less and a maximum whole body averaged specific absorption rate (SAR) of y for z min of MRI. The ABZ stent should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than x Tesla.
>
> In this testing, the stent produced a temperature rise of less than x degrees C at a maximum whole body averaged specific absorption rate (SAR) of x W/kg for z minutes of MRI.
>
> MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

<u>Overlapping Stents or Stents with Fractured Struts</u>

In addition to the above description of force, torque, and heating testing on the stent, FDA recommends that your labeling also describe whether you determined the effect of heating in the MRI environment for overlapping stents or stents with fractured struts. If you have not determined what those effects are, we recommend that your labeling reflect this, for example:

The effect of heating in the MRI environment for overlapping stents or stents with fractured struts is not known.

Drug-Eluting Stents

In addition to the above description of force, torque, and heating testing on the stent, FDA recommends that your labeling also describe whether you determined the possible effects of heating in the MRI environment on the drug and polymer coating. If you have not determined what those effects are, we recommend that your labeling reflect this, for example:

The effect of heating in the MRI environment on the drug or polymer coating is not known.

Stents not Tested for Heating

If you have determined the MRI compatibility of your stent with force and torque tests, but do not have heating test data, we recommend your labeling advise users of this, for example:

Non-clinical testing at field strengths of x T or less showed that the XYZ stent should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than x Tesla.

This device has not been evaluated for heating in the MRI environment.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

Drug-Eluting Stents not Tested for Heating

If you have tested your drug-eluting stent for force and torque successfully, but have not determined the effect of heating, we recommend that your labeling describe the testing and results, for example:

Non-clinical testing at field strengths of x T or less showed that the XYZ stent should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than x Tesla.

This device has not been evaluated for heating in the MRI environment. The effect of heating in the MRI environment on the drug or polymer coating is not known.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

Literature Review with No Testing for 316L Stainless Steel or Nitinol Stents

For a 316L stainless steel or nitinol stent, if you have not conducted testing for migration or heating, but have provided comparisons to published test results in your PMA, your labeling should reflect that MRI compatibility is based on literature, for example:

> Although comparisons to published test results indicate that the YZX stent may not migrate in the MRI environment at field strengths of x T or less, the YZX stent has not been tested for safety in the MRI environment. Therefore, MRI scans should not be performed on patients post-implantation until the stent has completely endothelialized to minimize the potential for migration. For a conventional uncoated 316L stainless steel (or nitinol) stent, this period is usually considered to be 8 weeks.
>
> This device has not been evaluated for heating in the MRI environment.
>
> MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

We recommend basing your MRI compatibility labeling on testing instead of literature for drug-eluting stents or stents with indications where MRI is used to rule out common adverse events, for example, carotid stenting where MRI is used to look for strokes shortly after implantation. FDA believes that you should perform MRI compatibility testing for these stents to ensure that these patients are not refused medically-indicated MRI scans because the stent labeling indicates a lack of MRI compatibility testing.

Modified Stainless Steel Stents

A modified stainless steel stent is one that is a revised version of an approved device. Your labeling should reflect whether the cold work has been modified as in the examples below.

> **<u>Modified Stainless Steel Stents with Unchanged Cold Work</u>**
>
> If you demonstrate that the amount of cold work in your modified stainless steel stent has not significantly changed from a design used in an approved stent, you should label the stent to indicate that while the stent has not been tested, it is comparable to previous devices, for example:
>
> > Although comparisons to other devices marketed in the US indicate that the X stent may not migrate in the MRI environment at field strengths of x T or less, the XYZ stent has not been tested for safety in the MRI environment. Therefore, MRI scans should not be performed on patients post-implantation until the stent has completely endothelialized to minimize the potential for migration. For a conventional uncoated 316L stainless steel stent, this period is usually considered to be 8 weeks. This device has not been evaluated for heating in the MRI environment. MRI image quality may be compromised if

the area of interest is in the exact same area or relatively close to the position of the stent.

Modified Stainless Steel Stents with Modified Cold Work

If the amount of cold work in your stent has significantly increased from a design used in an approved stent, we recommend that you perform appropriate testing as described in section **VII. Non-Clinical Tests, B. Stent Dimensional and Functional Attributes, 11. Magnetic Resonance Imaging (MRI) Safety and Compatibility** and describe the results in your labeling, for example:

Non-clinical testing at field strengths of x T or less showed that the XYZ stent should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than x Tesla.

This device has not been evaluated for heating in the MRI environment.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

No Literature Review and No Testing – 316L or Nitinol

If you have not tested your 316L or nitinol stent or compared it to published literature, we recommend your labeling reflect this, for example:

The ABC stent has not been tested for safety in the MRI environment. Therefore, MRI scans should not be performed on patients post-implantation until the stent has completely endothelialized to minimize the potential for migration. For a conventional uncoated 316L stainless steel (or nitinol) stent, this period is usually considered to be 8 weeks.

This device has not been evaluated for heating in the MRI environment.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

As stated above, we recommend basing your MRI compatibility labeling on testing instead of literature to ensure that certain patients are not refused medically indicated MRI scans because the stent labeling indicates a lack of MRI compatibility testing.

MRI Compatibility Based on Animal Testing

If you have performed animal testing that shows that your stent does not damage tissue at a specific SAR, your labeling should reflect this, for example:

Animal histology results for the X stent showed no significant tissue damage at a maximum whole body average specific absorption rate (SAR) of x W/kg for z minutes of MRI.

However, if you did not assess the effect of heating on the drug or polymer coating of a drug-eluting stent, your labeling should reflect this, for example:

> Animal histology results for the X stent showed no significant tissue damage at a maximum whole body average specific absorption rate (SAR) of x W/kg for z minutes of MRI. The effect of heating in the MRI environment for overlapping stents or stents with fractured struts is not known. The effect of heating in the MRI environment on the drug or polymer coating is not known.

G. Overview of Clinical Studies

You should provide a narrative description of the pivotal study or studies and any supporting or feasibility studies relevant to the stent. The narrative should be brief, and should include the following information for each study:

- whether the study was a pivotal, supporting, or feasibility study
- the design of the study, including any randomization, blinding, and the control or controls used
- the number of patients enrolled
- the number of investigational sites both inside the United States (US) and outside the United States (OUS)
- the primary study endpoint or endpoints
- the amount of available follow-up
- the total planned follow-up.

H. Adverse Events

Observed Adverse Events

You should provide a brief narrative statement about the source or sources of the adverse event experience followed by results in a tabular format. In the table, we recommend that you present adverse events using a "per protocol" (also known as an "evaluable") approach.

In this approach, the numerator consists of the number of patients presenting with the adverse event during or before the analysis window. For each adverse event, the denominator consists of:

The number of patients evaluated during the analysis window	+	Any patients not evaluated during the analysis window, but that had the specified adverse event between treatment and the analysis window

The numerator consists of the number of patients presenting with the adverse event during or before the analysis window.

You may also use an alternative approach known as "intent-to-treat" analysis, in which any patients not evaluated during the analysis window are assumed to have had an adverse event. If your trial involves substantial numbers of crossover patients, an intent-to-treat analysis may be more appropriate. In this analysis, adverse events would be assigned to the original treatment group regardless of actual treatment received or time at which the adverse event occurred.

You should include an adverse events table that captures data through the longest available follow-up for the study. You should also provide protocol definitions for adverse events as footnotes, or a reference to definitions included with the Principal Safety and Effectiveness Table.

We have provided a list of suggested elements for inclusion, below. Additional elements may be appropriate given the specific vessel or vessels to be stented.

Coronary Indications

You should separate in-hospital events from out-of-hospital events (through X days or months), for categories such as:

Major Adverse Cardiac Events (MACE), which includes:

- Death
- Q-wave Myocardial Infarction (MI)
- Non-Q-wave MI
- Emergent Coronary Artery Bypass Grafting (CABG)
- Target Lesion Revascularization (TLR)

Target Vessel Failure (TVF)

Target Vessel Revascularization (TVR)

TVR, non-TLR

Stent Thrombosis (acute, subacute, late)

Cerebro-Vascular Accident (CVA)

Bleeding complications

Vascular complications

Peripheral Indications

You should separate in-hospital, out-of-hospital, and cumulative events for categories such as:

Major Adverse Event (MAE) – may be study specific

- Death
- Q-Wave MI (in-hospital)
- Non-Q-Wave MI
- End organ injury or ischemia or both
- TLR

TVF

TVR

TVR, non-TLR

Stent thrombosis (acute, subacute, late)

Bleeding Complications

- Access Site
- Non-access site

Vascular Complications

- Perforation
- Aneurysm
- Pseudo-aneurysm
- Dissection

Potential Adverse Events

You should include potential adverse events associated with stenting of the intended coronary or peripheral vessel or vessels.

I. Clinical Studies

You should include additional specifics about the clinical studies described in the section titled "Overview of Clinical Studies," above. We suggest the following format:

Purpose/Objective

You should state the intent of the study, including the primary endpoint or endpoints.

Conclusions

You should briefly state the study outcome or outcomes.

Design

You should describe your study design. The following is a partial list of elements that may be appropriate to your design:

- whether the design is randomized or non-randomized
- whether the study is controlled
- which type of controls were used
- if the study results were compared to objective performance criteria (OPCs)
- how any OPCs were derived.

You should also describe the success criteria for the trial (i.e., superiority or non-inferiority when compared to the control).

You should include a brief description of patient entry criteria, such as:

- vessel location
- vessel size

- vessel type, (i.e., *de novo* or restenotic)
- type of evaluations (clinical, telephone, angiographic/intravascular ultrasound follow-up).

Demographics

You should describe characteristics of your patient populations that could affect the results of the study, including:

- age
- race
- gender
- percentage of smokers
- incidence of hyperlipidemia
- previous MI
- diabetes
- any other important covariates.

Methods

You should describe any use of a Clinical Events Committee, a Data and Safety Monitoring Board, and/or a core laboratory for adverse event adjudication, as appropriate.

Results

You should briefly describe the results of the study, including whether the primary endpoint or endpoints were met, for example:

> The X stent demonstrated a lower rate of MACE as compared to the control group (X% vs. Y%, $P<0.001$).

You should refer to the Principal Safety and Effectiveness Table, which is described in the next section of this guidance.

J. Principal Safety and Effectiveness Table

We recommend that you present the clinical outcomes in a tabular format as "effectiveness measures" and "safety measures," separately or combined. Your data presentation should follow the same approach used for adverse event reporting (for example, per protocol or intent-to-treat). You should include protocol definitions for terms used in the table.

You should provide Kaplan-Meier estimates for relevant endpoints in your safety and effectiveness table, which may include, but are not limited to:

- MACE-free survival
- MAE-free survival

- TVF-free survival
- TVR-free survival
- TLR-free survival
- primary, primary assisted, and secondary patency survival.

In some instances, it may be appropriate to provide a graphical presentation of the most appropriate Kaplan-Meier survival endpoints (see examples of these endpoints below) and accompanying life tables. We believe that statistical comparisons between groups are only appropriate for randomized trials. The review branches are available to advise you on this issue.

Examples of Kaplan-Meier survival endpoints

- "Freedom from MACE" for coronary and peripheral stenting studies
- "Patency survival" for peripheral stenting studies

If you provide a survival graph, it should include error bars representing a standard error (SE) of ± 1.5. The scale should either begin on the y-axis at a value greater than zero – we recommend using a value around 50 - 60 % – or indicating a break in the scale to illustrate the differences in survival curves, if applicable.

Updates to Principal Safety and Effectiveness Table

For some devices, updates to the Principal Safety and Effectiveness Table to reflect additional clinical follow-up beyond the primary follow-up interval are identified as a condition of PMA approval. In this case, the updated labeling should be submitted as a PMA supplement.

If such an update is not listed as a condition of approval, you may provide the updated labeling in your annual report, as long as the updated information is based on the endpoints and follow-up schedule prospectively defined in your clinical study protocol. For updates that relate to new indications, see 21 CFR 814.39.

If clinical results in the updates raise a safety or effectiveness concern when compared to the initial results of your study, we recommend that you update the labeling to reflect this new information.

K. Patient Selection and Treatment

We recommend that this section provide information related to individualization of treatment.

L. Directions for Use

You should include directions for proper preparation and use of the device in this section of the labeling. If multiple delivery systems are available, you should clearly indicate differences specific to the delivery system. An example would be to indicate the difference between an over-the-wire (OTW) and a rapid exchange (RX) delivery system.

Compliance Chart (Balloon Expandable Stents Only)

Pre-mounted Balloon Expandable Stents

You should include a compliance chart that provides the average stent inner diameter following deployment at various pressures derived from bench testing. You should display the data as determined from testing. However, if you round the data, you should footnote the chart to indicate that the data is rounded. We recommend the format presented in Table 5 (see section **VII. Non-Clinical Tests, C. Delivery System Dimensional and Functional Attributes, 4. Stent Diameter vs. Balloon Pressure**).

Un-mounted Balloon Expandable Stents

You should include general recommendations, which you may base on clinical study balloon inflation pressures and engineering testing, to provide guidance to users about the relationship between inflation pressures and stent inner diameter.

Percent Foreshortening (Self-Expanding Stents Only)

You should provide a table that shows:

- vessel lumen diameter
- unconstrained stent diameter
- percent foreshortening.

If you base your values on mathematical calculations, you should indicate this in a footnote to the table. See section **VII. Non-Clinical Tests, B. Stent Dimensional and Functional Attributes**, **3. Foreshortening**, for information on testing stent percent foreshortening.

M. Patient Materials

You should provide examples of patient materials, such as the patient guide and implant card, that you will make available. See also **Guidance on Medical Device Patient Labeling**, http://www.fda.gov/cdrh/ohip/guidance/1128.html.

Appendix A: Test Summary Checklist
(continued on next page)

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Test		Sizes Tested and Sample Sizes	Test Method or Standard Reference	Accept/Reject Criteria	Results
Material Characterization	Material Composition				
	Shape Memory and Superelasticity				
	Mechanical Properties				
	Corrosion Resistance				
Stent Dimensional and Functional Attributes	Dimensional Verification				
	Percent Surface Area of the Stent				
	Foreshortening				
	Recoil for Balloon Expandable Stents				
	Stent Integrity				
	Radial Stiffness and Radial Strength				
	Stress Analysis				
	Fatigue Analysis				
	Accelerated Durability Testing				
	MRI Safety and Compatibility				
	Radiopacity				
	Coating Durability *(coated stents only*)				
	Crush Resistance (*peripheral indications only*)				
	Kink Resistance (*peripheral indications only*)				

Appendix A: Test Summary Checklist (*continued from previous page*)

Test		Sizes Tested and Sample Sizes	Test Method or Standard Reference	Accept/Reject Criteria	Results
Delivery System Dimensional and Functional Attributes	Balloon Rated Burst Pressure (*balloon expandable stents only*)				
	Balloon Fatigue (*balloon expandable stents only*)				
	Stent Diameter vs. Balloon Pressure (Compliance Chart) (*balloon expandable stents only*)				
	Catheter Bond Strength				
	Crossing Profile				
	Balloon Inflation and Deflation Time (*balloon expandable stents only*)				
	Stent Securement for Unsheathed Stents				
Biocompatibility	Biocompatibility				

Appendix B: Applicable Standards

A list of FDA-recognized standards is available at
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

ISO Standards
10993 Biological Evaluation of Medical Devices
25539-1 Cardiovascular Implants – Endovascular Devices • Part 1 – Endovascular Prostheses, Annex D – In vitro Testing and Reporting

ASTM Standards
F746 Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials
F748 Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices
F2004 Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Alloys by Thermal Analysis
F2052 Standard Test Method for Measurement of Magnetically Induced Displacement Force on Passive Implants in the Magnetic Resonance Environment
F2079 Standard Test Method for Measuring Intrinsic Elastic Recoil of Balloon expandable Stents
F2081 Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents
F2082 Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Shape Memory Alloys by Bend and Free Recovery
F2119 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants
F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices
F2182 Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging
F2213 Standard Test Method for Measurement of Magnetically Induced Torque on Passive Implants in the Magnetic Resonance Environment
G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes